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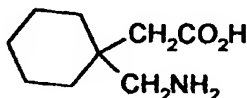
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(54) Title: AN IMPROVED PROCESS FOR THE PREPARATION OF GABALACTAM



(1)



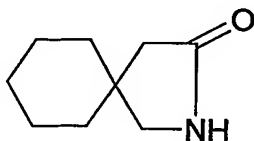
(2)

(57) Abstract: This invention relates an improved process for the preparation of gabalactam. Gabalactam is chemically known as 2-azaspiro(4,5)decan-3-one. Gabalactam has the structural formula 1 given.

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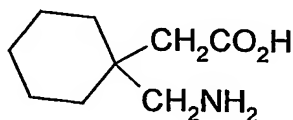
AN IMPROVED PROCESS FOR THE PREPARATION OF GABALACTAM

This invention relates an improved process for the preparation of gabalactam. Gablactam is chemically known as 2-azaspiro(4,5)decan-3-one. Gabalactam has the structural formula 1 given below.



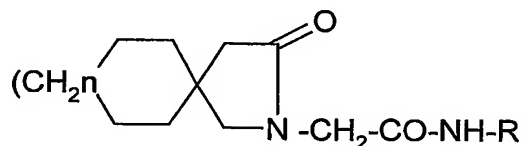
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Gabalactam is useful as a starting material for the well-known anti-epileptic and analgesic, 1-aminomethylcyclohexane-1-acetic acid, commonly known as gabapentin which has the structural formula 2.



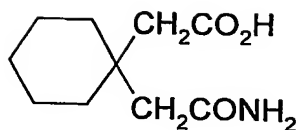
2.,

It is also a starting material for some of the compounds of structural formula 3



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wherein R is a hydrogen atom or a saturated or unsaturated lower aliphatic radical and n is 0,1 or 2 reported in US 4228179, with antiepileptic activity. Gabalactam of the formula 1 was first synthesized by Sircar in the laboratory in 1928 (J. Ind. Chem. Soc., 1928, 5, 549; Chem. Abstracts, 1929, 23, 818). Specifically, Sircar carried out a Hofmann Reaction on the mono amide of cyclohexane-1,1-diacetic acid of the formula 4



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with alkaline sodium hypobromite at 55 degrees centigrade for 2 hours. The reaction solution was acidified with HCl and evaporated to dryness. The residue was washed with ether to remove free organic acids and then extracted with acetone. The acetone extract was evaporated to dryness. The residue was neutralized with alkali and extracted into ether. Evaporation of this extract is claimed to give gabalactam in 46% yield.

The process published by Sircar (1928) though not hazardous, results only in 46% yield of gabalactam. The process is not useful for the commercial manufacture of gabalactam because of the number of steps involved and the low yield of gabalactam., making the process expensive and unviable for commercial production of gabapentin for which gabalactam is the penultimate and crucial intermediate .

But some commercial processes for its preparation have appeared later (US patent nos 4152326 & 5091567 equivalent to PCT Int. Application no 9914184A & US patent no 5068413) which are explained below.

US patent no 4152326 discloses that treatment of N-benzene sulfonyloxy-1,1-cyclohexane di acetic acid imide with an alcoholic solution of sodium ethylate gives gabalactam.

US patent no 5091567 (and PCT Int. Application 9914184A) discloses that gabalactam can be made from cyclohexanone in 3 steps:

1. Addition of the Wittig Reagent from triethylphosphono acetate to cyclohexanone to give ethyl cyclohexylidene acetate.

2. Addition of nitromethane to the ethyl cyclohexylidene obtained to form ethyl 1-nitromethylcyclohexane acetate and

3. Catalytic reduction of the nitro methyl derivative.

US patent 5068413 discloses that gabalactam can be obtained from cyclohexanone in 4 steps as follows:

1. Conversion of cyclohexanone into diethyl cyclohexylidene malonate.
2. Addition of cyanide to form diethyl 1-cyanocyclohexyl malonate.
3. Hydrolysis of diethyl 1-cyanocyclohexyl malonate to 1-cyanocyclohexyl malonic acid and
4. Catalytic hydrogenation of the 1-cyanocyclohexyl malonic acid at elevated temperature resulting in decarboxylative lactamisation.

Thus, in the processes described in US patent no 5091567 and PCT Int. Application no 9914184A, hazardous nitromethane and costly wittig reagents are used. An explosive and inflammable hydrogen gas and pyrophoric catalyst such as 10% Pd-C are used in the third step.

In US patent no 5068413; the disadvantages are handling of highly poisonous sodium cyanide in the second step and use of expensive rhodium or pyrophoric Raney Nickel as catalyst in the final step.

US patent no 4152326 suffers from the fact that one needs to handle corrosive benzene sulfonyl chloride and sodium ethoxide, both of which are toxic inflammable re-agents.

Very recently a process for the preparation of gabapentin has been disclosed in the Indian Patent 182685, In the Example 1 given in the said

patent for the preparation of crude 1(amino methyl) cyclohexane acetic acid hydrochloride (commonly known as gabapentin hydrochloride), a reference has been made to the preparation of 2-aza spiro(4,5) decane -3 one (commonly known as gabalactam) by using standard Hoffman reaction conditions starting from the amide of the formula 4. When we followed the said procedure for the preparation of 2-aza spiro(4,5) decane -3 one (commonly known as gabalactam), the process gave very unsatisfactory results as explained below .

We carried out the Hoffmann reaction on the amide of the formula 4 using bromine and varying strengths of sodium hydroxide solution. At the end of the reaction, the solution was acidified with HCl. The acidic solution was extracted with methylene chloride and the methylene chloride layer evaporated to dryness. The residue which has been stated to be gabalactam in the Example 1 of the said patent, was actually a thick gum showing the presence of gabalactam by analytical methods such as HPLC . This product did not solidify even upon seeding with standard gabalactam, which is a very nice crystalline solid, melting at 88-92 deg C. The gum was also found to be highly acidic and upon neutralization with alkali, gabalactam was liberated in the solid form. It thus appeared that the product extracted from the acidified Hoffmann Reaction solution might be the **hydrochloride** of gabalactam and not gabalactam itself as has been stated in the Example 1 of the said patent. The gummy product was subjected to HPLC. Although gabalactam was found to be the major component, other impurities were present, one of them more polar with a RRT (Relative Retention Time) to a significant extent. Area % purity was determined in three experiments and in one (namely Example no 1) gabalactam content (wt%) was also determined. The results are given below:

No.	Amide of The formula 4 In grams	Wt (g) & strength (%w/w) of NaOH Solution	Bromine in ml	Yield of Gummy product	Purity as Gabalactam area %
1.	100	215 40	26	49	85*
2.	200	430 50	52	73	72
3.	100	215 73	26	70	85

* Gabalactam content 42g.

The results of the above experiments very clearly indicate that under the conditions described in the Indian Patent 182685 the yield and the purity of 2-aza spiro(4,5) decane -3 one (commonly known as gabalactam) obtained is no better than the initial experiments described by Sarcar in 1928. Further the Example is silent on the yield and purity of 2-aza spiro(4,5) decane -3 one. Therefore the said Indian Patent does not fulfill the need for a process for synthesizing the important & crucial intermediate Gabalactam in higher yields(more than 70 %) and of high purity(more than 95%) , which are essential conditions for its production commercially so that the process can be used directly for the preparation of Gabapentin.

Upon more detailed investigations, we observed, surprisingly that the highly alkaline solution (pH 11-13) from the Hoffmann Reaction already contained free gabalactam of the formula 1 which could be conveniently extracted into nonpolar hydrocarbon solvents like toluene, ethylene dichloride, methylene dichloride and hexane.. Aqueous washing of the organic layer followed by evaporation gave a major crop (more than 55%)

of gabalactam. The alkaline layer was heated again and worked up with organic solvents to give more of the lactam to offer a total yield of more than 70% by theory. Since the lactam was extracted from a highly alkaline solution, acidic impurities, which are significant contaminants in the previously disclosed acidic workup according to the process disclosed in the above Example 1 mentioned Indian patent, are avoided, conferring an additional advantage of higher purity (more than 95% by HPLC).

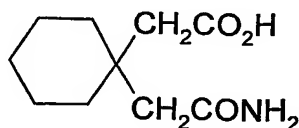
Accordingly, the present invention provides an improved process for the preparation of gabalactam of the formula 1



1

Which comprises

- (i) Preparing an aqueous solution of an alkali or alkaline earth hydroxide in a concentration ranging from 10 to 20% by weight,, adding bromine to the resulting solution to give the appropriate alkali or alkaline earth hypobromite solution having a concentration ranging from 5 to 10% by weight ,
- (ii) adding 1 part by weight of an amide of the formula 4



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- to 7.5 to 9.5 parts by weight, of the solution of the alkali/alkaline earth hypobromite obtained in step (i) during a period in the range of 1 – 4 hours, at a temperature in the range of –10 to + 10 degrees C ,
- (iii) Keeping the resultant mixture for ageing in the temperature in the range of –10 to +10degree C for a period in the range of 0.5 to 2 hours,
- (iv) Heating the mixture gradually to a temperature in the range of 80 to 100 degrees C , for a period in the range of 3 to 8 hours,
- (v) Cooling the reaction mixture to a temperature in the range of 30 to 50 degrees C,
- (vi) Extracting the mixture using a nonpolar solvent or a mixture thereof,
- (vii) Subjecting the resulting organic layer washed aqueous layer to the steps of (iii) to (v) defined above
- (viii) Combining the organic layers obtained in steps(v) & (vi) together
- (ix) Washing resulting combined organic layers with water at a temperature in the range of 30-35 degree C and
- (x) Distilling of the organic solvent at a temperature in the range of 60-110 deg C, under reduced pressure.

In a preferred embodiment of the present invention the various steps in the process can be carried out as follows

In the step (i), preferably an alkali hydroxide, more preferably sodium hydroxide may be used, The concentration of the solution may preferably range from 10 to 15% more preferably 12.5%. The concentration of the hypobromite may preferably be in the range of 5 to 8 % and more preferably 7% by weight.

In the step (ii) the amount of hypobromite added may preferably be 8 to 9 parts, more preferably 8.5 to 9 parts of the solution of sodium hypobromite. The addition may be effected preferably during a period ranging form 1 – 3 hours, more preferably 1-2 hours. The temperature during the addition may be maintained at preferably –5 to +5 degrees C, more preferably –5 to 0 degrees C , and aging the reaction mixture in the

temperature in the range of -5 to -0 degree C ,preferably for a period in the range of 0.5 to 1.5 hrs and more preferably for 1 hr.

In step (iii) the heating is effected preferably at 80 to 90 degrees C, more preferably 80 to 85 degrees C. The heating is effected preferably during a period of 4 to 6 hours, more preferably for 4 hours

In step (iv) the cooling is effected to a temperature preferably in the range of 35 to 45 degrees C , more preferably 40 degrees C ,

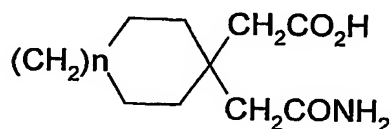
In step (v) the extraction is done using preferably an aliphatic or aromatic hydrocarbon solvent such as ethylene dichloride, methylene dichloride, hexane and toluene and more preferably an aromatic solvent like toluene.

In step (vi) the organic solvent extracted aqueous layer is once again heated to a temperature in the range of 80-100 deg C during a period of 3-8 hrs, aged for 5-8 hrs cooled and re-extracted with toluene .

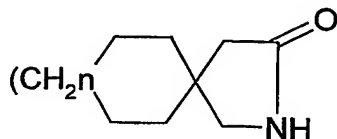
In an embodiment of the invention the combined organic layers is treated with charcoal for removing any coloring matter present in it

In step (vii) the distilling of the organic solvent is done preferably between 60-90 deg C and more preferably between 60-65 deg C

It would be clear from the above description that the process of the present invention could be advantageously employed for the conversion of amides of the general formula 5



Where n represents a value of 0 to 2 to Lactams of the general formula 6



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Where in 'n' is an integer with a value of 0-2.

Thus the process of the present invention is found to be very useful for the preparation of gabalactam commercially in the view of the fact that the process straight away yields highly pure (more than 95 %) gabalactam in yields greater than 70% of theory.

This process while avoiding the usage of toxic reagents like cyanides, pyrophoric catalysts, sodium ethoxide and high energy water evaporation processes, yields the gabalactam in a simple, extraction process using low cost material such as bromine and sodium hydroxide. As explained earlier the process of the present invention gives gabalactam of purity over 95%.

The details of the invention are given in the Examples given below which are provided to illustrate the invention only and therefore cannot be constructed to limit the scope of the invention.

Example – 1

Bromine (0.824 kg, 5.15 mole) is added to a solution of sodium hydroxide (1 kg) in water (7 l) at -5 to 0 degrees C over 45 – 90 min and the solution stirred for an additional 30 min at the same temperature. Cyclohexane-1, 1-diacetic acid monoamide of the formula 3 (1 kg, 5.02 mole) is added to the above solution in portions over a period of 3 hrs at -5

to 0 degrees and the mixture stirred at the same temperature for 1 hr. The reaction mass is heated to 80 –85 degrees C slowly over a period of 4 hrs and stirred for another 6 hrs at the same temperature. It is then extracted with toluene after cooling the reaction mixture to 40 degree C twice. The aqueous layer is again heated at 80 – 85 degrees C , aged for 6 hrs at the same temperature, cooled to 40deg C and extracted with toluene twice. The toluene layers are combined, treated with charcoal and filtered. The filtrate is washed with water twice and evaporated at a temperature of 60-65 deg C under vacuum to give white crystals of gabalactam of the formula 1 (0.62 kg, 80.7%), m.p. 88-90 degree C ; purity (area % by HPLC greater than 99).

Example – 2

Bromine 42g (0.257 mole) is added to a solution of potassium hydroxide (80g/80% purity) in water (350ml) at –5 to 0 degrees C over 60 min and the solution stirred for an additional 30 min at the same temperature. Cyclohexane-1,1-diacetic acid monoamide of the formula 3 50g (0.251 mol) is added to the above solution in portions over a period of 2 hrs at –10 to 0 degrees C and the mixture stirred at the same temperature for 2 hrs. The reaction mass is heated to 90-98 degrees C slowly over a period of 4 hr and stirred for another 5 hrs at the same temperature. It is then extracted with ethylene dichloride twice, after cooling the reaction mixture to 30 degrees C . The aqueous layer is again heated at 90-98 degrees C and extracted with ethylene dichloride after cooling the reaction mixture to 30 degrees C , twice. The ethylene dichloride layers are combined, treated with charcoal and filtered. The filtrate is washed with water and evaporated under reduced pressure to give brownish white crystals of gabalactam of the formula 1 (28g, 72.8%) m.p. 88-90 degree; purity (area % by HPLC 98).

Example – 3

Bromine 45g (0.257 mole) is added to a solution of sodium hydroxide (45g) in water (350ml) at -10 to 0 degrees C over 45 – 90 min and the solution stirred for an additional 30 min at the same temperature. Cyclohexane-1,1-diacetic acid monoamide of the formula 3 (50g, 0.251 mole) is added to the above solution in portions over a period of 1 hr at -5 to 0 degrees C and the mixture stirred at the same temperature for 1 hr. The reaction mass is heated to 80 –90 degrees slowly over a period of 6 hrs and stirred for another 8 hrs at the same temperature. It is then extracted with methylene dichloride twice, after cooling the reaction mixture to 30 degrees C . The aqueous layer is again heated at 80-90 degrees and extracted with methylene dichloride after cooling the reaction mixture to 30 degrees, twice. The methylene dichloride layers are combined, treated with charcoal and filtered. The filtrate is washed with water and evaporated under reduced pressure to give white crystals of gabalactam of the formula 1 (28g 72.8%) m.p. 88-90 degree; purity (area % by HPLC 99).

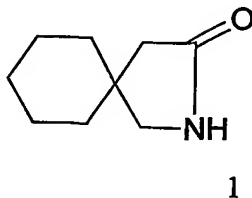
Example 4

Bromine 50g (0.285 mole) is added to a solution of sodium hydroxide (55g) in water (300ml) at -10 to 0 degrees C over 45 – 90 min and the solution stirred for an additional 30 min at the same temperature. Cyclohexane-1,1-diacetic acid monoamide of the formula 3 (50g, 0.251 mole) is added to the above solution in portions over a period of 1.5 hrs at -10 to 0 degrees C and the mixture stirred at the same temperature for 1 hr. The reaction mass is heated to 85-95 degrees slowly over a period of 5 hrs and stirred for another 7 hrs at the same temperature. It is then extracted with toluene twice, after cooling the reaction mixture to 50 degrees C . The aqueous layer is again heated at 85-95 degrees C and extracted with

toluene after cooling the reaction mixture to 50 degrees C, twice. The toluene layers are combined, treated with charcoal and filtered. The filtrate is washed with water and evaporated under reduced pressure to give white crystals of gabalactam of the formula 1 (29.5g 76.7%) m.p. 88-90 degree C ; purity (area % by HPLC 98).

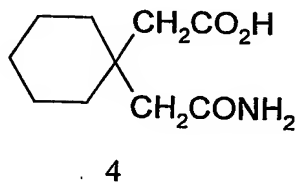
We Claim

1. An improved process for the preparation of gabalactam of the formula 1



Which comprises

- (i) Preparing an aqueous solution of an alkali or alkaline earth hydroxide in a concentration ranging from 10 to 20% by weight,, adding bromine to the resulting solution to give the appropriate alkali or alkaline earth hypobromite solution having a concentration ranging from 5 to 10% by weight ,
- (ii) adding 1 part by weight of an amide of the formula 4



- to 7.5 to 9.5 parts by weight, of the solution of the alkali/alkaline earth hypobromite obtained in step (i) during a period in the range of 1 – 4 hours, at a temperature in the range of -10 to + 10 degrees C ,
- (iii) Keeping the resultant mixture for ageing in the temperature in the range of -10 to +10degree C for a period in the range of 0.5 to 2 hours,
- (iv) Heating the mixture gradually to a temperature in the range of 80 to 100 degrees C , for a period in the range of 3 to 8 hours,
- (v) Cooling the reaction mixture to a temperature in the range of 30 to 50 degrees C,
- (vi) Extracting the mixture using a nonpolar solvent or a mixture thereof,

- (vii) subjecting the resulting organic layer washed aqueous layer to the steps of (iii) to (v) defined above
 - (viii) Combining the organic layers obtained in steps (vi) & (vii) together
 - (ix) washing resulting combined organic layers with water at a temperature in the range of 30-35 and
 - (x) Distilling of the organic solvent at a temperature in the range of 60-110 deg C, under reduced pressure.
2. An improved process as claimed in claim 1 wherein in the step (i) the alkali used is an alkali hydroxide, more preferably sodium hydroxide
3. An improved process as claimed in claims 1 & 2 wherein in the step (i) the concentration of the alkali / alkaline earth solution is in a range from 10 to 15% more preferably 12.5%.
4. An improved process as claimed in claims 1 to 3 wherein in the concentration of the hypobromite is in the range of 5 to 8 % and more preferably 7% by weight.
5. An improved process as claimed in claims 1 to 4 wherein the amount of hypobromite added is in the range of 8 to 9 parts, more preferably 8.5 to 9 parts of the solution of sodium hypobromite.
6. An improved process as claimed in claims 1 to 5 wherein the addition is effected during a period ranging from 1 – 3 hours, more preferably 1-2 hours.
7. An improved process as claimed in claims 1 to 6 wherein the temperature employed during the addition is maintained at preferably –5 to +5 degrees C, more preferably –5 to 0 degrees C

8. An improved process as claimed in claims 1 to 7 wherein the aging of the reaction mixture is effected at a temperature in the range of -5 to -0 degree C, preferably for a period in the range of 0.5 to 1.5 hrs and more preferably for 1 hr.
9. An improved process as claimed in claims 1 to 8 wherein in the step (iii) the heating is effected preferably at a temperature in the range of 80 to 90 degrees C, more preferably 80 to 85 degrees C.
10. An improved process as claimed in claim 9 wherein the heating is effected during a period of 4 to 6 hours, more preferably for 4 hours
11. An improved process as claimed in claims 1 to 10 wherein the cooling is effected to a temperature in the range of 35 to 45 degrees C, more preferably 40 degrees C,
12. An improved process as claimed in claims 1 to 11 wherein the extraction is done using an aliphatic or aromatic hydrocarbon solvent such as ethylene dichloride, methylene dichloride, hexane and toluene and more preferably an aromatic solvent like toluene.
13. An improved process as claimed in claims 1 to 12 wherein the organic solvent extracted aqueous layer is once again heated to a temperature in the range of 80-100 deg C during a period of 3-8 hrs, aged for 5-8 hrs cooled and re-extracted with toluene.
14. An improved process as claimed in claims 1 to 13 wherein the combined organic layers is treated with charcoal for removing any coloring matter present in it

15. An improved process as claimed in claims 1 to 14 wherein the distilling of the organic solvent is done preferably between 60-90 deg C and more preferably between 60-65 deg C

INTERNATIONAL SEARCH REPORT

International application No

PCT/IN 02/00225

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D209/54

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

CHEM ABS Data, EP0-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	SIRCAR S S G : "The Preparation of the Substituted Butyrolactams" JOURNAL OF THE INDIAN CHEMICAL SOCIETY, THE INDIAN CHEMICAL SOCIETY, CALCUTTA, IN, vol. 5, 1928, pages 549-554, XP009011251 ISSN: 0019-4522 cited in the application page 550, line 22 -page 552, line 35 ---	1-15
A	US 4 024 175 A (SATZINGER GERHARD ET AL) 17 May 1977 (1977-05-17) column 1, line 1 -column 2, line 35; examples 1,4 --- -/--	1-15

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

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Date of the actual completion of the International search

30 May 2003

Date of mailing of the International search report

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Name and mailing address of the ISA

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INTERNATIONAL SEARCH REPORT

International Application No
PCT/IN 02/00225

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 5 091 567 A (HERRMANN WOLFGANG ET AL) 25 February 1992 (1992-02-25) cited in the application column 1, line 65 -column 5, line 61; claim 1; examples 1,2,8 -----	1-15

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